UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/703,350	10/31/2000	Fuad Mehraban	10716-15 (CURA-90/P1891R1	3065

23552 7590 06/28/2007

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
06/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/703,350	MEHRABAN ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56 and 69-80* is/are pending in the application.

4a) Of the above claim(s) *80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56 and 69-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/21/2007, 4/11/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

The request filed on 4/11/2007 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 09703350 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 1-55, 57-68 are cancelled. Claims 78-80 are added. Newly submitted 80, drawn to a method of inhibiting PMA-induced angiogenesis of endothelial cells by administering to said endothelial cells an antibody, which is directed to an invention that is independent or distinct from the invention originally claimed method, inhibiting angiogenesis in a tumor, because inhibiting PMA-induced angiogenesis of endothelial cells is involved in treatment in vitro, which is distinct from treating an angiogenesis by administrating an antibody in the mammal (now amended to the tumor) in vivo. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 80 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. In addition, it is noted that applicant has amended base claim 56 from "...administering to the mammal..." to "...administering to the tumor...", which is still treated as in vivo inhibiting angiogenesis as originally presented invention.

Thus, claims 56 and 69-80 are pending. Claims 56 and 69-79 are examined on the merits.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 2/21/2007 and 4/11/2007 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56 and 69-79 are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of inhibiting angiogenesis in a tumor comprising administering to the tumor an effective amount of an antibody or antigen binding fragment thereof that specifically binds and neutralizes a polypeptide comprising SEQ ID NO:76 or binds to an immunogenic fragment of SEQ ID NO:76. Although applicant has amended claims from originally presented "*inhibiting angiogenesis in a mammal comprising administering to the mammal an antibody*" to currently presented "*inhibiting angiogenesis in a tumor comprising administering to the tumor an antibody*", the Office is examining the claims as originally presented invention as in vivo method of inhibiting angiogenesis in a tumor because original claimed term "administering to the mammal" is drawn to an in vivo method.

The specification teaches that protein of SEQ ID NO:76 is a secreted glycoprotein referred to as a stanniocalcin precursor (page 25). The specification proposes "neutralizing antibodies to stanniocalcin may be useful as therapeutic molecules because they bind to stanniocalcin and thereby remove it from the immediate cellular environment". Thus, the specification appears to broadly claim that the claimed antibodies would predictably provide a therapeutic benefit to humans in need of reducing angiogenesis.

For example, the specification teaches that angiogenesis is an important component of a variety of diseases and disorders including tumor growth and metastasis, rheumatoid arthritis, psoriasis, diabetic retinopathy, neovascular glaucoma, etc. (page 12). Thus, the claims broadly encompass methods of treating cancer by administering an antibody that binds to SEQ ID NO:76. However, the specification lacks critical guidance and objective evidence to predictably enable those of skill in the art to practice the invention with success. For example, there is no evidence that inhibition of stanniocalcin activity or removal of the secreted glycoprotein of SEQ ID NO:76 results in the inhibition of angiogenesis with concomitant reduction of tumor cell growth in a mammalian subject. There is no guidance that selective binding of SEQ ID NO:76 with an antibody would predictably reduce tumor cell growth or metastasis in a mammalian subject. The state of the art currently still considers that reducing tumor cell growth and inhibiting disorders associated with angiogenesis is highly unpredictable. For example, Mook et al., (Biochim Biophys Acta, vol 1705:69-89, 2004, abstract) recently comment on treating cancer by inhibition of angiogenesis by inhibiting the function of the proteins, gelatinases regulation of MMP-2 and MMP-9, involved in angiogenesis stating "*MMP-2 and MMP-9 activity regulates bioavailability and activity of growth factors and cytokines, affects the immune response and is involved in angiogenesis. Because of the multifunctionality of gelatinases, it is unpredictable at what stage of cancer development and in which processes gelatinase activity is involved. Therefore, it is concluded that the use of MMP inhibitors to treat cancer should be considered carefully*". Thus, just with regards to inhibiting angiogenesis in general, there is a high standard of accountability recognized by those in this particular area. Based on the very little guidance in the specification, one of skill in the art would not immediately presume that the antibodies would successfully reduce angiogenesis.

Moreover, the pharmaceutical administration of antibodies for the treatment of tumors requires a high degree of guidance as those of skill in the art recognize the unpredictability of treating mammals (including mammals with tumors) via the administration of antibodies. Dillman R. O., (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999)

provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43). Again, treatment of cancer in general is at most unpredictable, as underscored by Gura et al., (Science, v 278, 1997, pp.1041-1042, provided in previous office action) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of these underscores the criticality of providing workable examples, which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Thus, despite evidence that expression of the stanniocalcin gene is upregulated under endothelial tube-forming conditions and the mRNA is found in cancer tissues, the specification offers no guidance and or objective evidence that "inhibiting" or neutralizing this activity in a mammal or a tumor would effectively inhibit angiogenesis and treating a tumor.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Response to applicant's argument

The response filed 4/11/2007 has been carefully considered but is deemed not to be persuasive.

The response states:

"working examples will not by itself render the claimed invention non-enabled. MPEP § 2164.02. A basis provided in the Final Office Action for rejecting the claims is the alleged lack of a working examples. The Examiner asserts objective evidence such as a working example is "critical and necessary" for enabling one skilled in the art to make and/or use the claimed invention. The MPEP, however, specifically states the "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the ground of lack of enablement." MPEP § 2164.02".

and

Applicants teach, for example, that neutralizing antibodies to stanniocalcin are useful as therapeutic molecules because they bind to stanniocalcin and thereby inhibit stanniocalcin activity (page 25, lines 17-19). Applicants show expression of stanniocalcin was upregulated in endothelial cells undergoing tube formation (page 5).

In response to this argument, the Office agrees with application as indicated in MPEP§ 2164.02: working examples will not by itself render the claimed invention non-enabled. However, instant claimed invention claim a method that is unpredictable method of using an antibody in vivo for treating a tumor by inhibiting angiogenesis. The specification does not give any direction or guideline for one skilled in the art how to use the invention to inhibit tumor growth by administering such antibody to the protein of SEQ ID NO: 76. Showing expression of stanniocalcin was upregulated in endothelial cells undergoing tube formation and neutralizing antibody is an in vitro result and may be just an invitation for further research of using the antibody in vivo and further in clinic. The research is not guarantee that one skilled in the art can practice the antibody for inhibiting angiogenesis in vivo by administering the antibody for tumor treatment.

Applicant also argue:

"Applicants have shown that stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma vasculature. Stanniocalcin is not expressed in normal vessels". And "The combination of increased expression in endothelial cells, increased expression in tumor tissue and release of stanniocalcin during tube formation provides a reasonable correlation of the relationship of upregulation of stanniocalcin with angiogenesis in tumor tissues.

Applicant further argues that applicants' teachings are also confirmed by other research in the field (page 6).

In response to this argument, again, the application as well as arts providing an expression pattern of the STC-1 protein in tumor and cell line do not render an in vivo method of treating the tumor with an antibody to the STC-1 protein enabled because one skilled in the art have recognized 1) no guidance on or exemplification of any correlation between expression of the protein in endothelial cells and increased risk of developing tumor progression *in vivo*; 2) there is no evidence showing that the higher levels of mRNA of STC-1 detected by in situ of the carcinoma tissues contributes to the tumor

development; and 3) no objective evidence to show that the antibody to STC-1 protein could inhibit or prevent tumor formation or development. As discussed above and before, the pharmaceutical administration of antibodies for the treatment of tumors requires a high degree of guidance as those of skill in the art recognize the unpredictability of treating mammals (including mammals with tumors) via the administration of antibodies. The disclosure provided in the application is only an invitation or suggestion for one skilled in the art to further investigation for the in vivo use of the antibody to inhibit the function of the protein. Applicant has not provided guideline or direction or objective evidence to allow one skilled in the art to practice or use the claimed invention without undue experimentation.

Applicant also states that the Office fails to provide any explanation or reasoning as to why the claims lack enablement in view of applicant's rebuttal evidence and further argues:

"one of skill in the art would reasonably expect that an antibody that inhibits angiogenesis in vitro would inhibit angiogenesis in vivo. Antibodies that inhibit angiogenesis in vitro have been shown to inhibit angiogenesis in vivo. For example, anti-VEGF antibodies were known to inhibit angiogenesis both in vitro and in vivo and have been approved by the FDA for treating cancer" (page 6-7).

In response to this argument, the Office has provided arts and reasons, such as unpredictability of the invention, in previous actions and more above in this action indicating that an antibody functions to remove an activity of a protein in vitro does not guarantee that the antibody works in vivo for treating a condition which is not even known contributed by the abnormal expression of this protein, see above in the rejection.

Applicant further argue:

"pharmaceutical administration of antibodies to treat tumors in mammals was not unpredictable and methods for enhancing antibody tumor penetration and biodistribution were known at the time of filing of the present application. For example, Eccles, 2000, Breast Can. Res., 3:86-90 discloses that antibody penetration into solid tumors can be improved by removing the constant (Fc) region and preparing monomeric or dimeric antibody fragments such as Fab, F(ab')2, and scFV. Applicants describe such antibody fragments and methods for making the fragments in the specification"

In response to this argument, the issue of antibody penetration will not be discussed here because the STC-1 protein in the claimed method is a secreted protein and biodistribution of antibody or antibody fragment is not a major issue currently rejected under 35 USC § 112, enablement.

Since the disclosure lacks guidance, direction, and objective evidence, and since the claimed method is not predictable, one skilled in the art would be forced into undue experimentation to practice the claimed invention. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained and made again above.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure, which has been disclosed before and again below.

Olsen et al., (US Patent Appl, pub, US2002004237A1, 10/27/999) teach a method treatment of diseases or disorders associated with neovascularization by administration of the stanniocalcin polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of stanniocalcin (para 422). Olsen et al., do not specifically teach or suggest that upregulation of stanniocalcin is associated with angiogenesis or angiogenetic tumor. Olsen et al., do not teach or suggest a method of inhibiting angiogenesis by administering an antibody to stanniocalcin.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600